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Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed 10/04/2003 in respect of Patent Application No.355/MUM/2003 of (a) VINOD CHINTAMANI MALSHE, 1, Staff Quarters, UDCT Campus, Matunga, Mumbai – 400 019, India, an Indian National, (b) PADMA VENKITACHALAM DEVARAJAN, 12, Staff Quarters, UDCT Campus, Matunga, Mumbai 400 019, India, an Indian National, and (c) SAYALEE RANJAN SHASTRI, 313/314, Amish Apartments, Opposite Kalwa Post Office, Kalwa, Thane – 400 605, India, an Indian National

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

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Dated this 9th day of August 2004.

(R.BHATTACHARYA)
ASST. CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See section 7]

1. We,

   (a) VINOD CHINTAMANI MALSHE

   (b) 1, Staff Quarters, UDCT Campus, Matunga Mumbai – 400 019. India

   (c) Indian National

   (a) PADMA VENKITACHALAM DEVARAJAN

   (b) 12, Staff Quarters, UDCT Campus, Matunga,
   Mumbai 400 019. India

   (c) Indian National

   (a) SAYALEE RANJAN SHASTRI

   (b) 313/314, Amish Apartments, Opposite Kalwa Post Office, Kalwa,
   Thane 400 605. India

   (c) Indian National

2. Hereby declare –

   (a) that we are in possession of an invention titled "NOVEL BIODEGRADABLE ALIPHATIC POLYESTERS AND PHARMACEUTICAL COMPOSITIONS AND APPLICATIONS THEREOF"

   (b) that the Provisional Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

Received Rs. 1500/- by Cash
Challan M.B.P.S. dt. 10/4/03
Info Entry No. 287 in the Register of Patents, Mumbai
10-4-03

2871 355

355/MUM/2003
10/4/2003

3. Further declare that the inventor(s) for the said invention are

(a) VINOD CHINTAMANI MALSHE

(b) 1, Staff Quarters, UDCT Campus, Matunga Mumbai – 400 019. India

(c) Indian National

(a) PADMA VENKITACHALAM DEVARAJAN

(b) 12, Staff Quarters, UDCT Campus, Matunga,
Mumbai 400 019. India

(c) Indian National

(a) SAYALEE RANJAN SHASTRI

(b) 313/314, Amish Apartments, Opposite Kalwa Post Office, Kalwa,
Thane 400 605. India

(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Malshe, Vinod Chintamani)

(Devarajan, Padma Venkitachalam)

(Shastri, Sayalee Ranjan)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Provisional specification (3 copies)
   (b) Statement and Undertaking on Form 3
   (c) Fee Rs.1500/- in cheque bearing No. 637655 dated 10th April March 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 10th day of April 2003

DR. GOPAKUMAR G. NAIR
Agent for the Applicant
GOPAKUMAR NAIR ASSOCIATES
Nair Baug, Akurli Road
Kandivli (East), Mumbai – 400 101

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION

[See section 10]

"NOVEL BIODEGRADABLE ALIPHATIC POLYESTERS AND PHARMACEUTICAL COMPOSITIONS AND APPLICATIONS THEREOF"

(a) **VINOD CHINTAMANI MALSHE**

(b) 1, Staff Quarters, UDCT Campus, Matunga Mumbai – 400 019. India

(c) Indian National

(a) **PADMA V. DEVARAJAN**

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(b) 313/314, Amish Apartments, Opposite Kalwa Post Office, Kalwa,
Thane 400 605. India

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The following specification describes the nature of the invention and the manner in which it is to be performed:

Novel Biodegradable Aliphatic Polyesters and Pharmaceutical Compositions and Applications Thereof

Technical Field

[001] The present invention relates to novel biodegradable aliphatic polyesters and pharmaceutical compositions and applications thereof.

Background and Prior Art

[002] With the increasing demand for biodegradable/biocompatible polymers, aliphatic polymers like poly-lactic acid, poly-glycolide, copolymers of lactide-glycolide are gaining importance. These polymers are synthesized mostly by either ring opening polymerization or by direct polycondensation technique. These polyesters are very expensive as compared to the other polymers, which are widely used. Because of its very high cost, these polyesters find very less commercial usage but because of the GRAS status, these polymers are in great demand.

[003] In the pharmaceutical field, the trend in drug delivery has been towards biodegradable polymer excipients for controlled release formulation and for implants as it would not require follow-up surgical removal once the drug supply is depleted. The most widely investigated and advanced polymer with regard to available toxicological and clinical data, are the aliphatic polyesters based on glycolide/lactide which include poly-lactic acid, poly-glycolide, copolymers of lactide-glycolide.

[004] US Patent 4,076,798 describes a high molecular weight polyester resin, the method of making the same and the use thereof as a pharmaceutical composition. However they suffer from high toxicity and therefore poor applications in dosage forms.

[005] US Patent 5,478,564 and US Patent 5,609,886 describe a preparation method for the microparticles of copolymers of lactic acid and glycolic acid for controlled release of water soluble pharmaceutically active agents.

[006] US Patent 5,585, 460 highlights a method for synthesis of high molecular weight aliphatic polyester of lactic acid and glycolic acid to obtain microparticles of the polyester containing the medicament for pharmaceutical application.

[007] US Patent 5,705, 197 describes methods for preparation of microparticles of vaccine and biologically active substances using poly-(D, L lactide co-glycolide)

[008] US Patent 5,718,922 discusses the use of microparticles of copolymers of lactic acid and glycolic acid for intravitreal injection containing antiviral agents fro CMV retinitis.

[009] US Patent 5,919,835 describes polymer blends of two or more polyanhydrides and polyester or their mixtures as a carrier for pharmaceutically active agent.

[010] US Patent 6,133,404 describes a biodegradable polymer containing at least one aliphatic dicarboxylic acid containing 2-14 carbon atoms and at least one aromatic or alicyclic carboxylic acid and one glycol. This polymer exhibits good mechanical strength and can replace pre-exisiting expensive aliphatic polyesters.

[011] US Patent 6,159,502 discusses microparticles of poly (lactic acid) and its copolymers coupled with a carrier for oral delivery of substances to the circulation or lymphatic drainage of the host. The carriers are mucosal binding proteins, bacterial adhesions, viral adhesions, toxic binding subunits, lectins, Vitamin B.sub.12 and analogues or derivatives of Vitamin B.sub.12 possessing binding activity to Castle's intrinsic factor.

[012] US Patent 6,201,072 highlights a biodegradable ABA or BAB type of triblock polymer of poly-(lactide-co-glycolide) and polyethylene glycol which possesses reverse thermal gelation properties. This polymer has been used for pharmaceutical applications.

[013] US Patent 6,296,667 use poly-lactic acid as a bone substitute and US Patent 6,338,859 uses poly-lactic acid, poly-glycolic acid, poly-(D-lactic acid), poly-(D,L-lactic acid), lactide/glycolide copolymers for micelle formation along with poly-vinyl pyrrolidone for the delivery of anti cancer drugs.

[014] US Patent 6,303,677 describes a method for preparing a method biodegradable polymer by using adipic acid or ester forming derivatives or terphthalic acid and C-2 to C-6 substituted alkanediols or C-10 cycloalkanediols. These polymers have been used for making moldings or are blended with starch to obtain to obtain molds.

[015] US Patent 6,511,748 mentions the use of PLA and PGA as core material in bioabsorbable fibers which are used for fracture fixation and spinal fusion.

[016] US Patent 6,515054 and related patents use filler along with the biodegradable to lower the cost of the polymer and to accelerate biodegradation.

[017] Patent Application WO 0055236 describes a method for synthesizing aliphatic polyesters using aliphatic dicarboxylic acids and aliphatic glycols. This polymer finds applications in various fields like food packing material, films, semi-expanded and expanded products, fibers, fabrics, composites with mineral and vegetable filler, bottles for food, cosmetics and pharmaceutical field.

[018] Poly-(lactide/glycolide) has been used to make films containing antibiotics for the insertion into the periodontal pocket as described in Journal of Controlled Release 3(1993), 137-146

[019] As discussed, this class of polyesters has been used in a wide range of pharmaceutical applications. However this class of polyester has two main disadvantages, high cost and limited hydrolytic stability because of high concentration of ester linkages on the backbone which leads to their hydrolysis in the presence of atmospheric moisture.

[020] Hence it is essential to have a polyester which is less expensive, hydrolytically stable, good mechanical properties, easy to synthesize, biodegradable, biocompatible and safe for use in living organisms.

[021] Fats undergo metabolism in the liver by beta- oxidation where two carbon atoms in the fatty acid chain are removed in each cycle and hence fatty acids with even number of carbon atoms are easily metabolized.

[022] Polyesters of diols containing even number of carbon of carbon atoms and diacids with even number of carbon atoms could be synthesized by conventional condensation polymerization technique, direct polymerization technique.

[023] As described above most of the patents described, use lactic acid and glycolic acid for biodegradable polyester formation. Lactic acid and glycolic acid being very expensive, poly-lactic acid, poly-glycolide and co-polymers of lactic acid and glycolic acid are very expensive and thus their usage is limited on a commercial scale.

[024] Other patents describe the use of diacids and diols for aliphatic polyester synthesis. However the toxicity and in-vitro biodegradation of these polymers is not extensively studied. Also the use of these polymers for pharmaceutical applications is not completely described.

[025] The present invention synthesis polyesters of diols and diacids which contain even number of carbon atoms, which are biodegradable and non-toxic to living animals and could be used for a wide pharmaceutical application at a much lower cost.

Objective

[026] An object of the present invention is to develop a pharmaceutical composition using aliphatic polyester which has good stability, excellent mechanical properties, is easy to synthesize, less expensive and biodegradable.

Summary

[027] A biodegradable aliphatic polymer is synthesized by conventional condensation polymerization method from a diol and diacid as the starting material, which contain even number of carbon atoms in the presence of a catalyst. Para-toluene sulphonic acid is used as the catalyst. Solid state condensation is carried out to increase the molecular weight.

[028] The polymer thus formed can be used for making various pharmaceutical formulations which include microparticles, injectable sustained release particles, molded implants, tablets, coating polymer for granules, films etc.

Detailed Description

[029] The present invention is related to development of various pharmaceutical compositions using biodegradable aliphatic polyester synthesized by conventional condensation polymerization technique from diols containing 2-20 carbon atoms and dicarboxylic acid containing 2-50 carbon atoms. The number of carbon atoms for diols and carboxylic acid is not a limiting factor but both containing even number of carbon atoms and terminal carboxy group is essential. The synthesis is carried out in two steps by using two different catalyst which are, para-toluene sulphonic acid in esterification step and Zinc acetate in condensation step.

[030] Aliphatic polyesters of various molecular weights could be obtained by this method by varying conditions in the condensation step.

[031] Aliphatic polyester synthesized by this method has good thermal stability and excellent mechanical properties. The in-vitro degradation of the polymer is carried out with the help of lipase and obtained low molecular weight compound. The synthesized class of polyester would undergo same degradation pattern in living animals.

[032] On determination as per OECD guidelines, the LD_{50} of the synthesized polymer was observed to be more than 2000 mg /kg of body weight when tested in male albino mice. When said polymer was administered for a prolonged period of time, no tissue accumulation is seen in mice indicating its biodegradanility in living animals. Hence this polymer could be used safely in all living animals.

[033] The biodegradability and safe toxic limits of theses aliphatic polyesters make them useful in pharmaceutical applications.

[034] The biodegradable aliphatic polyester obtained by this invention was used as the base for microcapsules. The sustained release microcapsules containing a water insoluble drug can be produced by preparing an oil/water suspension system, in which the medicament is embedded within the polymer particles, which forms the oil phase, and the aqueous phase contains stabilizing agents for the microparticles. The

stabilizing agent forms a thin protective layer around the droplets and hence reduces the extent of droplet coalescence and coagulation. The stabilizing agents, which could be used, are polyvinyl alcohol, polyvinyl pyrrolidone, alginate, gelatin, methyl cellulose, polyoxyethylene derivatives of sorbitan fatty esters [Tweens] and polyoxyethylene fatty ethers [Brij].

[035] The microparticles were prepared by either solvent –evaporation technique or solvent extraction technique. The microparticles thus formed by this method were made into various dosage forms for administration by the living animals. The dosage forms were tablets, sustained release granules filled in capsules, microparticulate implants for periodontitis, microparticulate implants for synovial joint and other such formulations. The polymer was used for coating the granules in order to get sustained action and for preparation of biodegradable stents.

[036] In addition to the microparticles, the polymer could be molded into different shapes by melting the polymer and dispersing the medicament to obtain implants for the sustained release of the medicament for prolonged period of time. The polymer implant could be in circular, cylindrical or any other molded form.

[037] The class of drugs which could be used are anti-hypertensives, analgesics, steroids, physiologically active peptides and / or proteins, anti-cancer agents, antibiotics, antifebriles, acesodynes, anti-inflammatory agents, expectorants, abirritants, muscle relaxants, epilepsy remedies, anti-ulcerative agents, anti-hyperchondriac agents, anti-allergic agents, hypotensive hydragogues, diabetes curatives, hyperlipemic remedies, anticoagulants, hemolytic agents, anti tuberculous agents, hormones, anesthetic antagonists, osteoclastic suppressants, osteogenic promotives, angiogenesis suppressors and or mixtures thereof.

Advantages

[038] The said aliphatic polyester is easy to synthesized and inexpensive to manufacture on a commercial scale.

[039] The synthesized polymer is readily biodegraded and does not show any toxic effect as it is metabolized by normal lipid metabolism in the liver of living animals.

[040] The said polymer can be easily made into various dosage forms of wide pharmaceutical applications containing several classes of pharmaceutically active agent.

Examples

The invention is illustrated by way of examples as follows,

Example 1

[041] A 500 ml three necked flask equipped with a stirrer and condenser was charged with ethylene glycol and sebacic acid in a molar ration of 2:1. 0.1% paratoluene sulphonic acid was added as the catalyst. The temperature was gradually increased up to 130° C with vigorous stirring. The reaction was continued until the distillation of water was completed. 1% zinc acetate was added to carry out the condensation reaction for building up the molecular weight. The reaction was carried out under high vaccum and at a temperature of 180° C. The polyester with the desired molecular weight was formed after 300 minutes of condensation reaction.solvent evaporation method was used to prepare microparticles in which pharmaceutically active agent to be encapsulated was added to 5% solution of polymer in dichloromethane. This solution was added to a 1% solution of stabilizers were already described earlier with stirring at 2000 rpm. Stirring was continued for one hour at room temperature to evaporate the dichloromethane. The microparticles were formed where collected by centrifugation and were dried in vacuum to give a dry powder.

Example 2

Methods for making a molded implant

[042] The polymer was melted and the pharmaceutically active agent was dispersed in the melted polymer, which was then poured into molds to form implants of desired size and shape.

Example 3

Methods for coating of granules

[043] A 1-5 % solution of polymer was made in dichloromethane. This solution was applied to the granules containing the active principle to be coated in a coater. The rate of coating was dependent on the final use of the granules.

Example 4

[044] The microparticles formed in example 1 were incorporated in a gel suitable for use in the treatment of periodontitis.

Example 5

[045] The microparticles formed in example 1 were administered sud-cutaneously or intra-muscularly for sustained action for the required period of time.

Example 6

[046] The aliphatic polyester was molded into stents after being with ablated laser.

Dated this the 10th day of April 2003

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